

## **REMARKS**

### **Status of the Claims**

Claims 1-38 were pending. Claims 1, 6 and 11 have been amended. Claims 4, 5, 8-10, 12-19 and 22-38 have been withdrawn without prejudice or disclaimer. Claims 1-3, 6-7, 11, 20 and 21 are currently under examination.

### **Amendments to the Claims**

Claim 1 has been amended to recite, "wherein the antibody is specific," instead of "which" to further clarify the claim.

Claims 6 and 11 have been amended to recite, "human leukocyte antigen-DR (HLA-DR)," to further clarify HLA-DR.

### **Amendments to the Specification**

The specification has been amended to correct a typographical error and to update the priority claim as requested in the Action on page 3.

### **Claims Objections**

On page 3 of the Action, claims 1-3, 6-7, 20 and 21 are objected to as being drawn to non-elected embodiments.

The Applicants submit that the elected species interleukin-4 receptor  $\alpha$  (IL-4R $\alpha$ ) is part of the Markush-type group claim consisting of interleukin-2 receptor  $\alpha$  (IL-2R $\alpha$ ), interleukin-4 receptor  $\alpha$  (IL-4R $\alpha$ ), and interleukin-15 receptor  $\alpha$  (IL-15R $\alpha$ ). According to MPEP ¶ 803.02, "Following [species] election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability... should \*\*>the examiner determine that <the elected species> is allowable, the\*>examination< of the Markush-type claim will be extended." Thus, the Applicants submit that the elected species is allowable and that the examination should be extended to include another species of the Markush-type group of claim 1.

In addition, the Applicants submit that claim 1 is a linking claim to the elected and certain non-elected claims. According to MPEP ¶ 809, “The linking claims must be examined with, and thus are considered part of, the invention elected. When all claims directed to the elected invention are allowable, should any linking claim be allowable, the restriction requirement between the linked inventions must be withdrawn. Any claim(s) directed to the non-elected invention(s), previously withdrawn from consideration, which depends from or requires all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability.”

The Applicants therefore submit that the claimed subject matter drawn to a non-elected species should not be withdrawn, or in the alternative should be reentered in the case once the linking claim is found to be in condition for allowance. [MPEP ¶¶ 809, 809.02, 809.02(a), 809.02(c), 809.03 and 809.04]. The Applicants respectfully request removal of the objection.

#### **Rejection of Claims Under 35 USC §112, 1<sup>st</sup> Paragraph**

On page 4, the Action asserts that claims 1-3, 6-7, 11, 20 and 21 are rejected under 35 USC §112, 2<sup>nd</sup> Paragraph, “as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.” The Action asserts that claims 1-3, 6-7, 11, 20 and 21 are indefinite for reciting “linked,” in claim 1.

The Applicants disagree with this rejection. The skilled artisan having read the claim language “a conjugate of an antibody *linked* to a ligand-binding region of a receptor subunit” would understand the metes and bounds of the claimed subject matter. The term “linked” as used in independent claim 1 and supported through out the instant application means, for example, that a ligand-binding region of a receptor subunit and an antibody may be covalently linked, non-covalently linked, fused, immunologically associated, associated via a linker molecule or linked via a single chain molecule. See for example: page 3 lines 9-13 of the application as filed which recites, “The targeting moiety may comprise a *covalent conjugate* in which the antibody is *covalently linked* to the ligand-binding region, a *fusion protein* of the antibody and the ligand-binding region, or a *bispecific antibody* that has a *first specificity* for a cellular antigen specific to a targeted cell and a *second specificity* for a rapidly internalizing receptor complex. Page 7 lines 14-16 recites, “constructs then can provide a

platform for the engineering of bifunctional single chain molecules that can link a second moiety (receptor or a single chain antibody) to the first to retarget effector cells or molecules.”

In addition, other examples of linked conjugates can be found on page 8 lines 1-10 where the application recites, “The antibody/receptor conjugate can be formed by covalently linking the antibody to the receptor, directly or through a short or long linker moiety, through one or more functional groups on the antibody and/or the enzyme, e.g., amine, carboxyl, phenolic, thiol or hydroxyl groups, to form a covalent conjugate. Various conventional linkers can be used, e.g., diisocyanates, diisothiocyanates, ... The antibody construct may bind one arm to either the ligand binding region or a site that is remote from the ligand-binding site *depending* on whether ligand will be employed in a given application. Page 8 lines 11-12 of the application recite, “... mix the antibody with the ligand-binding region in the presence of glutaraldehyde to form the antibody/receptor conjugate.” Page 8 lines 18-19 of the application recite, “More selective linkage can be achieved by using a heterobifunctional linker such as a maleimide-hydroxysuccinimide ester.” Page 8 lines 24-25 recite, “It is advantageous to link the ligand-binding region of the receptor subunit to a site on the antibody remote from the antigen binding site...” Page 9 lines 4-6 recite, “...the antibody/receptor conjugate comprises a bispecific antibody conjugate which is linked immunologically to the ligand-binding region of a receptor.” Page 9 lines 10-15 recite, “...the antibody/receptor conjugate comprises a fusion protein, in which a fusion sequence comprising antibody linked to a ligand-binding region of the receptor is expressed in a recombinant virion-based, mammalian expression system or other mammalian, insect, yeast or E. coli-based expression system. Suitable linkers for linking the antibody to the ligand-binding region are, for example, (GGSBS)3...”

The Applicants submit that the skilled artisan would understand the metes and bounds of the term “linked” as used in claim 1, therefore the rejection is improper. For the reasons and support presented above, the Applicants submit that the term “linked” in claims 2 and 11 is also definite. Because claims 2-3, 6-7, 11, 20 and 21 depend from claim 1 and contain all the elements of claim 1 plus additional elements, the Applicants submit that claims 1-3, 6-7, 11, 20 and 21 are in condition for allowance. The Applicants request removal of the rejection.

On page 4, the Action asserts that Claims 6 and 11 are indefinite for reciting the abbreviation “HLA-DR.” The Applicants have amended claims 6 and 11 to recite, “human leukocyte antigen-DR (HLA-DR)” to overcome the rejection. HLA-DR is one member of the family of human MHC (major histocompatibility complex) class II antigens. The Applicants request removal of the rejection.

**Rejection of Claims Under 35 USC § 103(a)**

On page 5-8, the Action asserts that claims 1-3, 6-7, 11, 20 and 21 are rejected under 35 USC § 103(a) as being unpatentable over Hu et al ( Cancer Research 56:4998-5004, November 1, 1996; hereinafter “Hu”) in view of Galizzi et al (JBC 264 (12):6984-6989, April 25, 1989; hereinafter “Galizzi”). The Applicants respectfully traverse this rejection.

The Action asserts on page 6 that Hu et al. teaches a targeting moiety comprising a fusion protein of the Lym-1 antibody and interleukin 2 (IL-2). Applicants note that this involves direct binding of the IL-2 *ligand* to the antibody, and not binding of any component of the IL-2 *receptor* to the antibody, as in the instant claims. The Action further asserts on page 7 that Galizzi et al. teaches that the ligand binding region of the IL-4 receptor  $\alpha$  and the IL-4 ligand are components of a rapidly internalized receptor system. However, Galizzi et al. merely discloses that the complex of IL-4 *ligand* bound to IL-4 *receptor* is rapidly internalized during a temperature shift from 4 to 37 °C. Thus, the skilled artisan, reading Hu et al. and Galizzi et al., would have had no motivation to achieve the claimed combination of an antibody bound to the alpha subunit of *receptor* for IL-2, IL-4 or IL-15. At most, the artisan reading the cited prior art would have been motivated to bind the IL-2, IL-4 or IL-15 *ligand* directly to an antibody. There is no teaching or suggestion cited anywhere in Hu et al. or Galizzi et al. to bind an alpha subunit of the IL-2, IL-4 or IL-15 *receptor* to an antibody to promote internalization. Nor would the skilled artisan, reading Hu et al. and Galizzi et al., have had any reasonable expectation of success in substituting the alpha subunit of the *receptor* for the *ligand* itself in the method of Hu et al.

Under MPEP 2142, “to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all

the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vacck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).” Each of these elements of a prima facie case of obviousness is missing from the cited prior art.

Applicants respectfully submit that none of the cited prior art references, alone or in combination, teach or suggest the combination of the alpha subunit of an IL-2, IL-4 or IL-15 *receptor* bound to an antibody to promote internalization. This element is nowhere disclosed in the cited prior art. Further, the Action cites to no suggestion or motivation in any of the cited prior art to make the claimed combination. If anything, the reference of Hu et al. teaches away from the claimed invention by leading the skilled artisan to conjugate antibodies directly to *ligands* for the receptors, not to the receptors themselves. Finally, since there is no indication in any of the cited prior art that direct binding of the *receptor* alpha subunit to an antibody promotes internalization into the cell, the skilled artisan would have had no reasonable expectation of success in achieving the claimed invention.

Because a prima facie case of obviousness has not been established, rejection of the claims under 35 U.S.C. §103 is improper. Reconsideration and removal of the rejection are respectfully requested.

#### **Double Patenting**

The Action asserts on page 9 that claims 1-3, 6-7, 11, 20 and 21 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 15-16, 20 and 30 of copending Application No. 11/368,296 (hereinafter, the ‘296 application), in view of Galizzi and Hu.

As discussed above, alone or in combination Galizzi et al. and Hu et al. fail to teach the element of an antibody bound to the alpha subunit of an IL-2, IL-4 or IL-15 *receptor*. This element is also absent from the ‘296 application, as acknowledged by the Action at page, 9 which states, “The claims in copending Application No. 11/368,296 do not teach that the peptide conjugated to the HLA-DR antibody is IL-4 receptor  $\alpha$ .” In contrast to the assertion of the Action, this deficiency is not made up for in the teachings of Galizzi et al. or Hu et al.

Since this element of the claimed subject matter is missing from all three of the references of Hu et al., Galizzi et al. and the ‘296 application, Applicants submit that a prima facie case of

obviousness has not been established and Applicants respectfully request removal of the Double Patenting rejection.

CONCLUSION

For the reasons stated above, the Applicants submit that claims 1-3, 6-7, 11, 20 and 21 are in condition for allowance.

Respectfully submitted,

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